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COMBINED INTELLIGENCE OBJECTIVES SUB-COMMITTEE

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PHARMAHOLOGISCHES INSTITUT DER FRIEDERICH-WILHELMS UNIVERSITAT, BERLIN.

Reported By

Lt. Col. H. CULLUMBINE, R.A.M.C. M. of S.

CIOS Target Number 24/264

Medical

COMBINED INTELLIGENCE OBJECTIVES SUB-COMMITTEE
G-2 Division, SHAEF (Rear) APO. 413

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Personnel of Investigating Team

Lt. Col. H. Cullumbine, R.A.M.C. M. of S.

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Pharmahologisches Institut der Friederich-Wilhelms Universitat, Berlin; evacuated to Kappeln a.d. Schlei Landwirtschaftschule.

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Target opportunity Item 24. Visited June 1945. WA-555 4 16

Personnel:

Professor Dr. Wolfgang Heubner	- Director of the Institute
Dr. Manfold Kiess	- Chief Assistant
Dr. Helene Wilhelmi	
Dr. Martin Behrens	- Army captain and late Assistant Professor of Bio-chemistry, University of Giessen.
Dr. Otto Steinert	- Army captain and research fellow.
Various technical assistants.	

The problems under investigation or studied during the War were as follows:-

1. The study of smoke clouds of solid substances

Tests with sprayed watery solutions have shown that large drops do not reach the lung and small ones are breathed out again. The problem was to define the size of the particles for sprayed dusts which would remain in the lung. The experiments were performed by Herren von Bergmann and Havemann.

Smoke was produced in a 10 m^3 chamber, chiefly by spraying solutions of the pigment "Lachschwarz" in benzine. By alteration of the concentration of the solution, and using different sizes of nozzle for spraying, the behaviour of smoke clouds of different composition has been determined.

The concentration of the smoke was determined by asperation through filters and subsequent coloremetric measurement and count-in the ultramicroscope. Both methods gave the mean particle weight. Further analysis was done by means of specially constructed centrifuges, through which the smoke cloud rotated in a stream 1 mm broad. Alteration of the number of rotations and the speed of the passing smoke cloud gave all the desired grades of sedimentation. Determination of the contents and the measurement of the particles of smoke passing to and from the centrifuge, gave the weight and number of particles which remained in the centrifuge.

Particle sizes were measured in terms of 10^{-15} cc as a unit of volume and 10^{-5} cm as a unit of length for the diameter of the particles. The difference between the biggest and the smallest particles amounted to a range of about 3 decimal places. The distribution of the log of the size of the particles followed a binominal curve.

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In some tests cats were used in an attempt to determine the size of the particles retained by the lung. This was a difficult problem because of

(a) the alternate to and fro movement of the air in the respiratory tract;
(b) the associated "whirling" of the airstream;
(c) the respiratory dead space;
(d) different animals react differently to being connected to the apparatus and assume different types of breathing.

Because of these difficulties very varied results were obtained and no conclusion could be reached.

However, a second substance - Adamsit - was tested systematically in smoke form. The cloud was analysed colorimetrically in U/V light using a photo-electric cell. Adamsit smoke clouds obeyed the same general laws as did "Lachschwarz" smokes. Some subjective trials on humans demonstrated the fact that smoke clouds composed of moderately sized particles produced greater irritation than clouds of similar concentration but composed of very small particles, as long as the smoke is inhaled directly after passing through the centrifuge. They did not succeed in obtaining smoke clouds with particles of one uniform size.

Smokes, which consist chiefly of coarse particles, became refined in time by the sedimentation of the largest particles while smokes, which consist chiefly of very small particles, grow coarse by the aggregation of the particles. Hence both types of smoke tend toward a similar medium-sized particle composition, and all dust smokes should show a similar distribution after about one hour.

Since the arrest of Dr. Havemann in September 1943 no further progress has been made in this work.

2. <u>The Toxicology of Explosives.</u>

This work was started because of the toxic diseases occurring in munition workers in war time, especially when manufacturing dinitrobenzol. These workers become cyanosed from the formation of methaemoglobin and this formation has been studied quantitatively in cats by means of Havemann's cyanide method using the photo electric colorimeter. The chemical reaction between phenylhydroxylamine and haemoglobin can be explained as a catalytic process via a radicle containing four nitrogen atoms. The different sensitivity of different animal species can be explained by the different speed of re-formation of methaemoglobin. The particular occurrence of cyanosis with dinitrobenzol, when compared with other similar aromatic explosives, especially T.N.T. was investigated by testing numerous derivatives on cats. It was shown that steeric hindrance by methyl groups was of decisive

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importance in the reduction of the nitro-connection to the corresponding phenylhydroxylamine in the tissues.

A rarer cause of cyanosis, i.e. the formation of verdoglobin (sulphaemoglobin verdohaemochromagen), was also studied. Kiese developed a method for its quantitative determination and this was employed in animal tests. It was also ascertained that there are several near-related substances with such a green colour.

The blood of munition workers also often showed the presence of "heinzkörchen" in the red blood cells, this being the first sign in the development of anaemia. The appearance in different species has been studied quantitatively, using electronicroscopic and chemical methods of analysis.

A series of therapeutic tests, using iron and various vitamins gave negative results.

Attempts to identify the onset of liver damage, in chronic poisoning with T.N.T. and dinitrobenzol in rats and dogs, before the appearance of symptoms failed. Liver function tests (Felix's method determining appearance of Hydroxyphenyl Pyruvic acid after feeding) were done at regular intervals, but it was concluded that liver damage could only be detected when other toxic signs were already apparent and often only just before the animal died.

Besides the aromatic nitro compounds, nitric esters such as nitroglycerol, ethylnitrate and methylnitrate were also tested. With these compounds, "Heinz körperchen" were often formed without the later production of anaemia, whereas, in tests with nitric esters, methaemoglobinaemia was formed but there was no formation of "Heinz körperchen".

3. The Blood pigment

Dr. Kriese worked out a method for measuring very small amounts of methaeglobin, depending upon the reduction with hydrosulphate after transformation of haemoglobin into carboxy haemoglobin and measurement of the absorption band with the yellow and green mercury band.

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The existence of a red coloured nitrate-methaemoglobin was denied by determining the dissociation constant of this compound.

In the formation of methaemoglobin by the action of chlorate, there is an interesting catalytic effect by the methaemoglobin, which apparently accelerates the transition of the slowly reacting chlorate into the quickly reacting chlorite or hypochlorite - an example of auto-catalysis (Jung).

With the electro-microscope Jung has examined the changes in the red blood cells occurring after poisoning with phenylhydrazine and phenylenedramine. He found them to be distinctly different from genuine "Heinz körperchen".

4. Toxicology of Sulphonamides:- The theory of Kallner in Stockholm re the origin of cyanosis after the administration of sulphonamides was tested by Kiese and Gaede and was not confirmed. The blood of cyantoci patients, under sulphonamide treatment was examined for oxyhaemoglobin, methaemoglobin, verdoglobin and reduced haemoglobin content. The sum of their individual spectrum-absorptions equalled the actual total absorption and therefore, the assumption of a new colour substance was not substantiated.

5. Enzymes and Pharmacological Effects:- In course of systematic tests with CO_2, Kiese found that some ferments have their activity influenced independently of the change in hydrogenion concentration. d-Aminacidoxydase and catalase are inhibited whereas the fenol-phosphatase is stimulated to activity by CO_2.

The maintenance of the haemoglobin-iron in the bivalent form, required for the continued production of methaemoglobin, requires "active reduction processes". Kiese found that these depend upon enzymatic reactions in the red cells themselves. Several enzyme systems are concerned. One is able to reduce haemoglobin with lactic acid as substrate and with the formation of pyrar-acemic acid. Another needs glucose as substrate. The reduction of haemoglobin and methaemoglobin by glucose takes place in two ways. In one pyroracemic acid is formed as a reaction product; in the other the reduction occurs via the formation of hexosemono-phosphate. The system in the red cells which reduces haemoglobin via hexasemonophosphate consists of the following components:- Coferment, Warburg's Zwischen ferment and Haemoglobin-reductase. The relative importance of the two methods of reduction of haemoglobin has a species variation. Thus, in humans, the reduction is mainly by glucose, in rabbits and guinea-pigs it is done principally by lactic acid.

The reduction of haemoglobin in the red cells can be accelerated by certain dye-stuffs e,g, Toluidine Blue, Methylene Blue. The catalytic effect is exerted only on the Coferment -

/Zwischenferment

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Zwischenferment - Haemoglobinreductase system. Probably the Haemoglobinreductase reduces the dye-stuff and the reduced dyestuff then reacts with Haemoglobin.

6. Toxicology of Plasmoquine

In treating chronic malaria, some physicians recommend large doses of plasmoquine, as well as giving it intravenously. In this respect two questions were raised:

(a) the cause of the cyanosis,
and (b) the limit of giving plasmoquine without danger.

The work is not complete but certainly single lethal doses do not cause cyanosis even when death does not occur for several days.

7. Tetranitromethane: This may exist in impure T.N.T. and hence some knowledge of its toxic effects seemed desirable. It has little effect on the skin, but, on subcutaneous injections, it produces marked oedema followed by necrosis. Healing occurs without much delay. Intravenously, lung oedema is produced, just as it does after inhalation, and it may lead to death. Haemoconcentration, methaemoglobinaemia and typical "Heinz körperchen" appear as well as other red cell changes. After death, the main histological finding is damage to the capillaries, especially in the lungs. The parenchyma cells of the lungs and kidney show cloudy-swelling and their nuclei are barely visible. However, in dogs, permanent hepatic damage after repeated intoxication could not be demonstrated by liver function tests.

8. Intoxication by Trichlortriethylamine:-

Dr. Riedel, using dogs, has assessed the value of various substances in the treatment of tracheo-bronchitis caused by the inhalation of trichlormethylene. Inhalation of such things as peppermint oil or tannin was ineffective. However, camomile-oil containing azulen as well as pure azulen in paraffin oil seemed to be effective. The experiments are proceeding.

The effect of trichlortriethylamine on the metabolism of starved dogs and on rats is also being studied by Fr.Dr. Wilhelmi.

Professor Werner Koll was also discovered in residence at Kappeln. Apart from his work on C.W. he gave the following general medical information.

Professor Werner Koll, former director of the Institute of Pharmacology, Danzig, had been consultant in Pharmacology to Professor Wolfgang Wirth at the Military Academy, Berlin. Before the War he had been working chiefly on analgesics and he continued this work for the first half of the War. His technique was to measure

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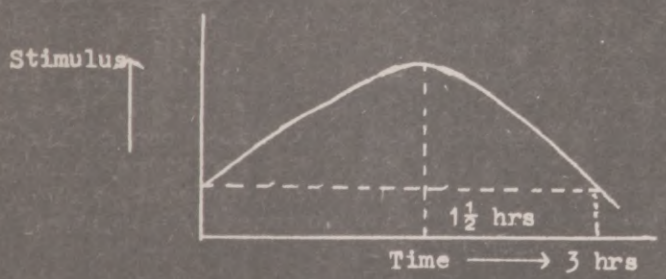
accurately the electrical stimulus required to produce toothache in dogs. (Lower animals were useless as it was impossible in them to distinguish between a simple reflex and a pain response). Wires were inserted through silver stoppings into the pulp of the Eye-teeth of dogs, the wires being inserted through a fistula in the cheek. The stimulus used consisted of repeated discharges from condensers - single shocks are not effective - using a fequency of 15/second and a duration of one second as a standard stimulus. This in dogs produced a reflex lowering of the lower jaw and a response to pain which was characteristic for each individual dog. The stimulus required remains constant for each dog over a considerable period of time and is measured by the voltage of the condenser charging.

After the injection of an analgesic the characteristic pain response of each animal remains unchanged but the stimulus required to produce it is increased. The course of analgesia has been followed through in this way e.g. for 1 mg/kg of morphine



Using this technique the following problems were tackled:-

(a) "The opium problem":- The alkaloids in opium, in the dosage they occur in opium, do not contribute much to raising the pain threshold. Morphine in a dosage of 1 mg/kg was used as standard and the dosages of the other alkaloids required to produce a similar raising of the pain threshold were determined. Codein has some analgesic effect but only in doses of about 10 mg/kg.

(b) Professor Wirth asked whether a mixture of morphine and pervetine (methyl benzedrine) had any analgesic effect. Professor Koll determined that the analgesic action of morphine was not depressed by pervetine but the narcotic action is neutralised. A mixture of 1 mg/kg morphine and 0.1 mg/kg pervetine was the optimum.

It was proposed to use this mixture for sitting wounded. It would relieve their pain without sending them to sleep, so that they could then be evacuated in a sitting position and transport space saved. Koll went as Consulting Pharmacologist

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to the 17th Army in June 1942 and he assessed the value of this mixture during the Caucasus offensive. He worked in collaboration with the Consulting Surgeon, Professor K.E. Frey. Ampoules containing a standard dosage of 20 mg morphine hydrochlor. and 7.5 mg pervetine were used.

This mixture, when injected subcutaneously into such wounded, produced a transient (half-an-hours) sleep and then the men were quite fresh and could be transported, without pain, for 4 or 5 hours in the sitting position.

It was also applied to the wounded in field hospitals where its effect could be more accurately assessed. Here it was concluded that the mixture had an action like morphine in intensity and duration, but that when the pain did return it could be tolerated better because the pervetine was still acting.

Lung wounds with pleural drainage, who lose fair amounts of protein, must eat but morphine depresses their appetite. With the morphine/pervetine mixture the patients were comfortable and still retained their appetite.

The mixture has the additional advantage of preventing circulatory collapse (unless too much blood has been lost) since the pervetine has an adrenaline-like action.

Other problems upon which Professor Koll gave his advice were:

(a) Spasmolytics - Atropine was reserved for the treatment of tabun since the stocks were low. Extract of belladonna and papaverine were also in short supply. Some synthetic drugs e.g. opaverine (Merck) were not very effective and so octinum, cesstrene etc. were suggested as substitutes.

(b) The store of Stropanthin was low and much of this was reserved for the possible treatment of phosgene cases. The C-glucoside of digitalis lanata (Cedilanid of Sandoz, Basle) was suggested as a substitute.

(c) The pure glucose (Merck) for intravenous use became in very short supply as the result of Allied bombing activity. What little remained was reserved for field use. The rear hospitals had to prepare their own solutions. Dextro-pure was not pure enough for intravenous injection, producing fever, rigors and xanthematous reactions. Work on this problem had just commenced when the Russians entered Danzig.

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Subcomm. Report # 81

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